UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,244	04/01/2004	Steven J. Soldin	31603-2049	6946

33721 7590 06/06/2008

TORYS LLP
79 WELLINGTON ST. WEST
SUITE 3000
TORONTO, ON M5K 1N2
CANADA

EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	PAPER NUMBER
1797	

MAIL DATE	DELIVERY MODE
06/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/814,244	SOLDIN, STEVEN J.	
	Examiner	Art Unit	
	Arlen Soderquist	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-2-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Applicant is advised that should claims 1-2 be found allowable, claims 31-32 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-27, 31-32, 34 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Each of the independent claims contains the limitation that the method/use "does not include any evaporation and reconstitution steps". Applicant failed to indicate where in the instant disclosure there is support for excluding these specific steps and examiner was not able to find such language. Thus, the newly added limitation is new matter.

4. Claims 15 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 15, it is not clear what elements constitute any of the three trademarked spectrometers. Additionally it is not clear if the claim would cover someone that has modified their spectrometer. Additionally, a trademark identifies a manufacturer or a producer, not a product. As an identifier of a company, a trademark is not a definite descriptor since the company can modify the product without changing its trademark name. In claim 37, it is not clear what constitutes the two systems listed and the trade names fail to define what is included in the two "systems" and the manufacturer can change the components without changing the name. In other words trade names and trademarks are not definite terms.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 28 is rejected under 35 U.S.C. 102(b) as being anticipated by Contin, Jayewardene, Korfmacher, Volosov (Clinical Biochemistry 2001, hereinafter called Volosov '01), Watt and Wong (all newly cited and applied).

In the paper Contin teaches a simple and rapid liquid chromatographic-turbo ion spray mass spectrometric determination of topiramate in human plasma. The method uses HPLC coupled with turbo ion spray mass spectrometry. Plasma sample pre-treatment was based on simple deproteinization by MeCN (acetonitrile, page 134, section 2.2). Liquid chromatography analysis was carried out on a reversed-phase column (C18, 125×4 mm I.D., 5 μm) using MeCN-ammonium acetate buffer, pH 6.3 as the mobile phase, at a flow-rate of 0.8 mL/minute (pages 134-135). Retention time for topiramate was 2.1 min. The detector was a single quadrupole mass spectrometer coupled to a turbo ion spray ion source and a heated nebulizer probe, operating in the pos. ion mode. Ion source temperature was off; voltage was +5800 V; nebulizer and curtain gas flow-rates were 6 and 10 mL/min, respectively. Calibration curves for topiramate were linear over the range 1 to 20 μg/mL. Absolute recovery ranged between 92 and 95%. Intra- and inter-assay precision was <4%. **The present procedure, omitting extraction and drying steps, is faster and simpler than the previously reported analytical methods for topiramate and possesses adequate sensitivity for routine therapeutic drug monitoring** in plasma from patients with epilepsy (first two paragraphs of page 134). Page 134 also teaches the preparation of standards.

In the paper Jayewardene presents an LC-MS-MS method for the determination of indinavir, an HIV-1 protease inhibitor, in human plasma. The analyte and internal standard are isolated from plasma by a simple acetonitrile precipitation of plasma proteins followed by centrifugation. LC-tandem mass spectrometry in positive ion, multiple reaction monitoring mode used pairs of ions at m/z of 614/421 for indinavir and 628/421 for internal standard, respectively. The calibration curve had a linear range from 3.0 to 12320 ng/ml when linear least square regression weighing 1/x was applied to the concentration versus peak area plot. The advantages of this method are the fast sample preparation, wide dynamic assay range and quick

analysis taking only 5 minutes for each sample run. The robust nature of this assay has been further verified during routine use over several months involving multiple analysts. The experimental section, on pages 310-311, teaches the mass spectrometer, reagents for precipitation and reagents for analysis.

In the paper Korfmacher teaches a systematic procedure for the dosing and liquid chromatography/atmospheric pressure ionization tandem mass spectrometric analysis of new chemical entities as part of new drug discovery. This report addresses the continuing need for increased throughput in the evaluation of new chemical entities (NCEs) in terms of their pharmacokinetic (PK) parameters by describing an alternative procedure for increasing the throughput of the in vivo screening of NCEs in the oral rat PK model. The new approach is called 'cassette-accelerated rapid rat screen' (CARRS). In this assay, NCEs are dosed individually (n = 2 rats/compound) in batches of six compounds per set. The assay makes use of a semi-automated protein precipitation procedure (page 337 including generation of standards) for sample preparation in a 96-well plate format. The liquid chromatography/atmospheric pressure ionization tandem mass spectrometry (LC/API-MS/MS) assay is also streamlined by analyzing the samples as 'cassettes of six'. Using this new approach, a threefold increase in throughput was achieved over the previously reported 'rapid rat screen'. Page 336 teaches the chromatography system and the mass spectrometer details. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

In the paper Volosov '01 teaches simultaneous simple and fast quantification of three major immunosuppressants by liquid chromatography-tandem mass spectrometry. The aim of the study was to develop a simple, fast, and universal method for the quantification of any combination of the 3 major immunosuppressants Sirolimus, tacrolimus, and cyclosporin in whole blood, using a LC-tandem mass spectrometer (API-2000, SCIEX, Toronto, Canada). 250 μL whole blood was spiked with internal standard (Ritonavir), and protein precipitated with 350 μL acetonitrile. The sample was centrifuged and 30 μL aliquot was injected onto the HPLC column, where it underwent an online extraction with ammonium acetate. After that, the automatic

switching valve was activated, changing the mobile phase to methanol and thereby eluting the analytes into the tandem mass spectrometer. The high selectivity of a tandem mass analyzer allows determination of any combination of the 3 drugs within a 5-minute run. Between-day precision was between 2.4% and 9.7% for all analytes at the concentrations tested. Accuracy ranged between 98.8% and 103.2% (n = 20). The method was linear over the measuring ranges of all analytes. Within-run precision was below %CV = 6% for all analytes. A good correlation with other analytical methods was observed. The simplicity, universality, and high throughput of the method make it suitable for application in a clinical laboratory. The method has been implemented in the laboratory for a routine use. The second to last paragraph of page 289 teaches that the method has the potential for use in different therapeutic areas due to its universality. A method similar to the described assay is currently being validated in their laboratory for quantification of antiretroviral drugs used for the treatment of AIDS. The experimental section on pages 286-287 teaches the mass spectrometer, reagents for precipitation and reagents for analysis.

In the paper Watt teaches higher throughput bioanalysis by automation of a protein precipitation assay with detection by LC-MS/MS. Generic methodology for the automated preparation and analysis of drug levels in plasma samples within a drug discovery environment was achieved through the redesign of a protein precipitation assay to a microtiter (96-well) plate format and the application of robotic liquid handling for performance of all transfer and pipetting steps. The first full paragraph of page 980 teaches that the methodology is for a wide range of analytes without compromising the data obtained. Validation studies revealed that the application of robotics to sample preparation, in general, maintained the analytical accuracy and precision compared with preparing samples manually. The use of rapid gradient LC-MS/MS for analysis coupled with flow diversion of the solvent front allowed the introduction of protein-precipitated samples into the mass spectrometer without the necessity for source cleaning. The problem inherent in automatically pipetting plasma, caused by fibrinogen clots, was overcome by storing samples at -80 °C and thus precluding clot formation. The resulting methodology allowed sample preparation for a 96-well plate designed to accommodate 54 unknowns, duplicate 12-point calibration curves, and 6 sets of quality controls at three levels in

approximately 2 hours. This approach allowed an increase in throughput of sample preparation and analysis to >400 samples per day per LC-MS/MS instrument with minimal manual intervention. Overall, substantial time savings were realized, demonstrating that automation is an increasingly essential tool in a drug discovery bioanalytical environment. The last full paragraph of page 979 teaches that several options for sample preparation are available to the analyst including solid phase extraction liquid-liquid extraction. The experimental section on pages 980-982 teaches the mass spectrometer, reagents for protein precipitation and reagents for analysis.

In the paper Wong teaches application of a liquid chromatography-mass spectrometry assay of a thiadiazole derivative in mice to pharmacokinetic studies. Modern atmospheric pressure ionization (API) ion-trap mass spectrometry in connection with fast chromatographic separations using a short narrow-bore C8 column was developed to determine 5-phenyl-3-thioureido-1,2,4-thiadiazole, a novel virus inhibitor in serum. Both the compound and an internal standard (I.S.) were separated from serum samples by acetonitrile deproteinization and extraction without time-consuming reconstitution. The chromatographic separation was achieved on a C8 reversed-phase narrow-bore column using acetonitrile-water-acetic acid (90:10:0.01, v/v/v) as a mobile phase. The mass spectrometric analysis was performed by atmospheric pressure chemical ionization (APCI) mode with positive ion detection. Single ion monitoring (SIM) scan mode of m/z 237 and 158 was used to quantitatively determine 301029 and I.S., respectively. The low limit of quantitation was 25 ng/ml. The assay exhibited a linear range of 25-2500 ng/ml. Recovery from serum proved to be 100-113%. The precision (C.V.) and accuracy (RE) of the method were 2-12% and 94-112%, respectively. The present method was applied to determine the pharmacokinetic parameters of the compound following oral administration of the agent to mice at 5 g/kg. The results revealed that the elimination half-life of the compound was 413 minutes and the area under serum concentration-time curve was 354 mug/ml/minute. Pages 56-57 teach the mass spectrometer, chromatography and reagents used. The first full paragraph of page 56 teaches that an HPLC method of thiadiazols included steps such as freezing and evaporation of the sample which may lead to degradation and sample loss (also see the conclusion paragraph on page 62).

7. Claim 38 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Lynch or Hamilton (both newly cited and applied).

In the paper Lynch teaches LC/MS determination of the intracellular concentration of two novel aryl phosphoramidate prodrugs of PMPA and their metabolites in dog PBMC. LC/MS assays were developed to determine the plasma and intracellular concentrations of two aryl phosphoramidate prodrugs of the nucleotide analog 9-[2-R-(phosphonomethoxy)propyl]adenine. LC/MS was used to demonstrate the presence of high concentrations of PMPA in peripheral blood mononucleocytes following oral administration of prodrugs in dogs. High concentrations of PMPA and active metabolite were detected in MT-2 cells incubated with prodrug using an ion-pairing LC/MS assay. The abstract/STN registry file at the end of the article shows that PMPA is another name for Tenofovir and thus the claim is clearly anticipated.

In the abstract Hamilton presents pharmacokinetics of tenofovir disoproxil fumarate in rhesus monkeys. The antiviral prodrug tenofovir DF (TDF) is being evaluated for treatment of HIV in phase III clinical trials. In preclinical development the pharmacokinetics (PK) of TDF were determined in rhesus monkeys and are here compared to human PK. Monkeys (3/sex/group) received a single 5.0 or 30 mg/kg intravenous (IV) bolus dose of tenofovir. Fasted monkeys (3/sex) received a single oral 250 mg/kg dose of TDF. One week later, oral TDF was dosed with food at 5.0, 50 or 250 mg/kg to the same groups of monkeys. Plasma samples obtained through 48 hours were assayed for tenofovir using LC/MS/MS (LOQ 1 ng/mL) and the data analyzed by non-compartmental methods. Following an IV 5 or 30 mg/kg tenofovir dose, mean peak plasma concentrations were 13.8+-3.08 and 79.0+-12.6 mg/mL, respectively, and declined biphasically with terminal half-lives (t1/2) of 5.37+-1.35 and 8.79+-2.79 hr. Mean AUC(0-inf) were 5.12+-1.15 and 38.4+-16.2 mgcntdothr/mL. Both Cmax and AUC were dose linear. Oral TDF gave tenofovir plasma mean Tmax values of 0.83-1.1 hr indicating rapid absorption and cleavage of the prodrug. Mean Cmax of 0.113+-0.042, 1.15+-0.676, and 1.68+-1.05 mg/mL were achieved in the 3 dose groups respectively, and declined biphasically with mean t1/2s of 8.23+-1.06, 8.54+-1.14, and 8.41+-1.20 hrs, respectively. Mean AUC(0-inf) were 0.725+-0.125, 6.38+-1.74, and 14.8+-7.81 mgcntdothr/mL. A comparison of Cmax and AUC values suggested dose linear PK between 5 and 50 mg/kg with statistically non-linear PK

between the 5 and 250 mg/kg doses. Conclusions: Similar oral bioavailability of TDF was observed between monkeys (32%, 5 mg/kg) and humans (25% fasted, 39% fed, 4 mg/kg) although no food effect was observed in monkeys. Tenofovir clearance was 4-5 fold faster in monkeys for both IV tenofovir and oral TDF compared with humans, with similar volume of distribution, suggesting faster renal clearance in monkeys.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 33 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bean (newly applied) in view of the admitted state of the prior art. In the paper Bean discusses therapeutic drug monitoring of antiretroviral agents. HIV+ patients fail antiretroviral therapy due to inadequate drug concentrations reaching the site of viral replication and/or the development of viral resistance to the antiretroviral agents. Adequate drug concentrations may not be reaching the virus due to poor compliance, poor absorption, or other pharmacokinetic factors such as metabolism, elimination, and drug interactions. The most important and most common pharmacokinetic drug interactions involve inhibition of metabolism, induction of metabolism, altered drug absorption, inhibition of renal excretion, and displacement from plasma protein binding sites. If a patient is failing antiretroviral therapy, TDM of antiretroviral agents could help in determining both adequacy of drug concentrations and patients' adherence. Ongoing studies will determine whether total drug concentration or free drug concentration (summary, page 22) of the protease inhibitors is the best predictor of response. Trough

concentrations could prove to be the most important predictor of response, but additional studies are needed to compare trough, peak, and AUC concentrations with response to treatment. Finally, if some patients fail therapy due to inadequate drug concentrations, then increasing the dose could benefit patients' outcome and increase longevity. Clinical trials are needed that compare patients who receive a fixed-dosage regimen with patients who have adjusted dose regimens. Such a study is the best way to determine the true value of TDM of the antiretrovirals. Page 22 also teaches an LC-MS-MS method for analyzing the antiretrovirals . Bean does not teach means to produce a sample of free antiviral drugs.

Paragraph [0070], page 19 of the instant specification, admits/teaches commercially available molecular cutoff filters such as the Amicon Centrifree micropartition system (Millipore Corporation, Bedford, Mass.) or the Worthington Diagnostics "ultrafree" system (Worthington, Jacksonville, Fla.) for obtaining free plasma drug concentrations.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure the free antiviral concentration as taught by Bean using sample produced with a known, commercially available system as admitted in the instant specification because of the possibility that the free drug concentration can be a better representation of the ability to determine the availability of the drug(s) as taught by Bean.

10. Claims 1-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shoup in view of Bean, Contin, Hamilton, Jayewardene, Korfmacher, Lynch, Volosov'01, Watt or Wong as described above. In the paper Shoup teaches simultaneous determination of six protease/reverse transcriptase inhibitors in human plasma utilizing LC/MS/MS. With the success of "combination therapies" using reverse transcriptase inhibitors, antiinfectives, and protease inhibitors in the treatment of HIV infection, BAS Analytics developed a single method for profiling six protease/reverse transcriptase inhibitors in human plasma. The method utilizes robotic solid phase extraction at neutral pH and is generally applicable to all the analytes and their internal standards. Page 19 gives the specifics on the tandem mass spectrometer. Page 21 gives data on the standards used. Shoup does not teach a method using protein precipitation without evaporation and reconstitution steps or the analysis of Tenofovir.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the Tenofovir of Hamilton or Lynch into the analysis method of Shoup because of its use in trials and analysis by mass spectrometric methods as taught by Hamilton or Lynch. It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace provide protein precipitation without evaporation and reconstitution steps as taught by Contin, Jayewardene, Korfmacher, Volosov'01, Watt or Wong because of the time savings, the reduced chance of degradation or sample loss or the generality/genericness of the protein precipitation method to prepare a variety of sample including those of AIDS drugs as taught by Contin, Jayewardene, Korfmacher, Volosov'01, Watt or Wong.

11. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art relates to mass spectrometry of compounds, some of which anticipate the instant claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (571)272-1265. The examiner can normally be reached on Monday-Thursday and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Arlen Soderquist/
Primary Examiner, Art Unit 1797